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PRINCIPAL INVESTIGATOR: Steven W. Lockley, Ph.D.

CONTRACTING ORGANIZATION: Brigham and Women's Hospital
Boston, MA 02115

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ABSTRACT

Epidemiological observations indicate that breast cancer risk is lower in visually impaired women compared to sighted women and that risk is inversely correlated with degree of visual impairment. A hypothesis to explain these findings is that blind people are less susceptible to suppression of melatonin by light exposure at night and therefore have higher levels of melatonin. Melatonin has oncostatic properties in vitro.

In a survey of 12,000 blind women, we will test the hypothesis that 1) the distribution of known reproductive risk factors for breast cancer among blind women will be consistent with lower risk when compared to the general population. In a subset of 240 women, we will test the hypotheses that 2) urinary melatonin levels are lower and estrogen levels are higher among blind women with light perception compared to women without light perception; 3) melatonin levels will be higher and estrogen levels lower among totally blind women who have non-24-hour melatonin rhythms and therefore a confirmed absence of light-induced suppression of melatonin, compared to totally blind women who have 24-hour melatonin rhythms and may be affected by light. Data collection is ongoing and there are no results to report at this time.

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INTRODUCTION

Since 1940, breast cancer incidence rates have been steadily rising in the United States (1). There is growing evidence for possible effects of exposure to light at night (LAN) on cancer risk due to the increased use of modern electric lighting (2-8). Epidemiological observations indicate that breast cancer risk is lower in women who are visually impaired as compared to the sighted population and that the risk may be inversely correlated with degree of visual impairment (9-13). One hypothesis proposed to explain these findings is that blind people are less susceptible to suppression of melatonin by light exposure at night and therefore have higher circulating levels of melatonin. Melatonin has been shown to have oncostatic properties in vitro (14). Frequent light-induced melatonin suppression has been hypothesized as a cause of the higher breast cancer incidence observed in female shiftworkers and flight-attendants (3-6,15-17). Blindness is also associated with disorders of the circadian system (18) and changes in reproductive function (19-20) which may also contribute to breast cancer risk. The aim of this study is to investigate further the relationship between the severity of blindness and melatonin and estrogen production while simultaneously assessing how blindness and/or melatonin production are related to known risk factors for breast cancer.

BODY

The study design and approved Statement Of Work is divided into two parts; Part 1 is an epidemiological health survey of breast cancer risk in 12,000 blind women and Part 2 is an assessment of melatonin and estrogen Levels in a subset of 240 blind women.

Part 1 – Epidemiological Survey of Cancer in the Visually Impaired

Task 1. All elements of Task 1 have been completed; a) We have finalized the epidemiology survey instrument (see Appendix A); b) Brigham and Women's Hospital Institutional Review Board approval has been obtained from the Partners Human Research Committee (HRC) (Protocol No. 2003-P-000263). Approval for the protocol has also been obtained from the Department of Defense (DOD) Human Subjects Research Review Board (HSRRB) (Log No. A-12744); c) We have published a request for volunteers in the American Council of the Blind (ACB) monthly publication 'Braille Forum' which has been circulated to ~26,000 visually impaired members (~13,000 women). We have also simultaneously published a request for volunteers in the National Federation of the Blind (NFB) monthly publication, "Braille Monitor" which has a circulation of ~50,000 (~25,000 visually impaired women); d) We have finalized the database structure and developed a web-based data input method to ensure consistency of data input and archiving from the range of media (Braille, print, audiotape, e-mail, electronic, web-based, telephone) that the data are being collected via; e) We have developed and finalized informed consent procedures for the range of media being used which have been formally approved by both the Partners HRC and the HSRRB.

Task 2. Task 2 is ongoing; a) We are in the process of recruiting for the epidemiological survey and obtaining informed consent. To date, informed consent for Part 1 of the study has been obtained from ~150 subjects; b) We are in the process of completing the survey with visually impaired volunteers. To date, ~150 blind women have completed the survey; c) We have developed a web-based data entry tool (see below for more details) and data entry is being performed online as data are collected. The database structure has been set up to allow automatic coding of the data during the data export process. We also investigated the development of adding Interactive Voice Response (IVR) to the media available but the hardware and support costs were prohibitive.

Part 2 – Assessment of Melatonin and Estradiol Levels in the Visually Impaired

Task 1. All elements of Task 1 have been initiated or completed; a) Approval has been obtained from the Partners Human Research Committee (HRC) (Protocol No. 2003-P-000263) and from the Department of Defense (DOD) Human Subjects Research Review Board (HSRRB) (Log No. A-12744); b) We have published a request for volunteers in the 'Braille Forum' and 'Braille Monitor' as described above; c) In conjunction with Mr. Brian Cade, Senior Bioinformatics Technician, we have developed a web-based data input method for sleep diary and actigraphy data to ensure consistency of data input and archiving from the range of media (Braille, print, audiotape, e-mail, electronic, web-based, telephone) that the data are being collected via. Incorporation of urine data into the database is ongoing; d) We have finalized informed consent procedures for

multiple media as described above; e) We have evaluated the range of equipment adapted for blind users and are in the process of ordering speaking kitchen scales. Other consumables are being purchased on an 'as-needed' basis.

Task 2. Task 2 is ongoing; a) We are reviewing our past and current databases of blind female subjects to invite them to volunteer in Part 2 of the study. Our past database includes more than 300 totally blind women who will be receiving a notice about the study within the next 2 months; b) We are in the process of recruiting for the home-based study and obtaining informed consent. To date, informed consent for Part 2 of the study has been obtained from ~70 subjects; c) The protocol and equipment required for the field-based study will be reviewed with subjects on an individual basis; d) The timetable for data collection is being reviewed on an individual basis; e-h) Elements e-h have not been completed to date. Urine sampling equipment will be sent to the first volunteers for Part 2 in the next month and the two-month assessment begun. Data entry will be completed upon return of the data and melatonin and estradiol assays will be scheduled.

Problems encountered in accomplishing the Statement Of Work

Although Task 1 for both study parts have been completed or initiated, they were not all completed within months 1-4 as originally proposed, and parts of Task 2 have not been completed in year 1 as scheduled. The main reason for this is the excessive delay in obtaining HSRRB approval for the project, without which we could not advertise for volunteers to participate or begin data collection. The long duration of time take to obtain HSRRB initial approval, and approval of subsequent amendments, has had a major negative impact on the progress of the project such that advertising for volunteers could not begin until April 2005.

An initial version of the study protocol was approved by Partners HRC on May 12, 2003, prior to the Idea award submission. Following several further Partners HRC-approved amendments and having obtained written confirmation from that Committee that our study involved minimal risk, the protocol was submitted to the HSRRB on February 5, 2004, more than three months in advance of the grant award date (May 15, 2004). I was notified that the documentation had been received but was not passed to the Regulatory Compliance group until March 8, 2004. I wrote to enquire as to the status of the HSRRB review on June 2, 2004 and was notified on June 22 that the review had not yet begun, more than a month after the grant award date. The Memorandum for Record (MFR) of the review was finally received on July 9. The protocol was amended as requested and resubmitted to HSRRB on September 15. The changes requested by the HSRRB also required approval by the Partners HRC and I was not given permission to submit those changes to the HRC until October 8. The institutional approval was obtained and returned to the HSRRB on November 23. Final HSRRB approval was obtained on December 3, 2004.

During this time, we had made further improvements to the epidemiological instrument and had submitted the changes to the HSRRB on January 25, 2005 and the Partners HRC approval of these amendments on February 1. HSRRB approval was obtained on March 1, 2005 and a call for volunteers was released in mid-April.

It would be beneficial to the program if the HSRRB review and approval process could be expedited in some way, particularly when an established HRC has reviewed the protocol and has designated the study to be of minimal risk.

Additional accomplishments

In addition to completion of the tasks outlined above, we have also made many additional advances which have further improved and supplemented the tasks outlined above.

a) In addition to obtaining the support of the American Council of the Blind (ACB), as described in our proposal, we have also obtained the support of the National Federation of the Blind for our study. In collaboration with Melanie Brunson, ACB Executive Director and Dr. Betsy Zaborowski, NFB Executive Director, we have developed a series of initiatives to advertise the study to their members and the wider visually impaired community including a) advertising the study via announcements and articles in their monthly publications 'Braille Forum' and 'Braille Monitor'; b) invitations to give a seminar/workshop at their 2005 annual conventions to discuss the background of the study and invite attendees to participate in the study; c) invitations and sponsorship of an exhibition stand at the 2005 annual conventions to be manned by BWH study staff to inform people about the study and conduct surveys at the convention; d) publication of the study web-site on the ACB/NFB web-sites and associated chapter list-servs; e) invitation for membership participation addressed to all State and local chapters of ACB/NFB. We attended the 2005 Spring meeting of the ACB Bay

State Council of the Blind and hosted an exhibition stand in the first of hopefully many such initiatives. These generous offers of help will greatly assist in communicating the study to blind women and recruiting volunteers.

b) In order to increase the number of media available for completion of the study, and widen the applicability of the study, we have developed the questionnaire for web use <www.bvihealthsurvey.bwh.harvard.edu>. The web-site is Section 508- and W3C-compliant as required for use by the visually impaired and allows visually impaired women to complete the study on-line at their own convenience. We established an advisory group of visually impaired computer users to ensure that the site was understandable, easy-to-use and compatible with the majority of screen-readers available to the visually impaired community. The advisory group also reviewed the survey and advised on the study questions, completion times, and ways to reduce open-ended questions. Two members of the advisory group also provided an on-line tutorial linked to the web-site in order to enable less experienced users to use the web-based tool. The web-site will also be used by the research team to input data and ensure that surveys completed in a range of media are collated easily into a single database. Subject- and researcher-entered data will be distinguished by study code.

The web-site and database was developed in collaboration with Velir Studios, Cambridge MA, who have provided more than $20,000 of pro bono services in support of the study. Velir worked with the research team and visually impaired advisory group in development of the website. The web-site and study database is hosted the Brigham and Women's Hospital Research Information Computing System (RICS) and Partners Information Systems at no charge. RICS will provide continuous technical monitoring and support for the study including data security, protection and back-ups and, in collaboration with Velir Studios, have developed develop HIPAA-compliant data collection and archiving procedures.

c) As outlined in the grant proposal, we have advertised for undergraduate volunteers to work on the study during the summer. We have selected eight students, six full-time amd two part-time, who have agreed to volunteer for the project (four from Harvard, two from Boston College, and one each from Boston University and Brown University). The students will assist in study advertising, subject recruitment, informed consent procedures, survey completion and identification of subjects for the field-based study. They will also attend one of the ACB or NFB national conventions to mann the exhibition stand and provide information to potential subjects. We have also prepared a seminar series to support their research efforts and the students will attend eleven weekly two-hour seminars given by leading researchers in the field of breast cancer, epidemiology and circadian biology.

Plan for Year 2 Statement Of Work

Part 1: The initial response from the study advertisements in the 'Braille Forum' and 'Braille Monitor' have not generated the number of responses expected. We aim to increase the recruitment effort in the following ways; 1) seminar and exhibition stand at the ACB and NFB national conventions at which ~2,500 visually impaired women will be present; 2) advertising via 150 radio reading services for the visually impaired nationwide; 3) mailshots to our database of more than 500 associations and institutions for the visually impaired; 4) advertisement of the study on list-servs for the visually impaired; 5) advertising and attendance at State and local chapters of the ACB and NFB.

Part 2: Recruitment for Part 2 will follow on from Part 1. In the initiatives outlined above, potential volunteers will be provided with information on both parts and to date, approximately half of the survey volunteers also volunteered for Part 2. In addition to new volunteers, the undergraduate students will also invite more than 300 blind women listed on a previous database to participate in the study and we anticipate that during the next year, we will study 160 blind women and therefore return to the recruitment schedule outlined in the Statement Of Work.

KEY RESEARCH ACCOMPLISHMENTS

- Established research collaboration with the two largest nationwide associations for the visually impaired; the American Council of the Blind and the National Federation of the Blind
- Development of web-based version of the survey for use by subjects and by study staff for data input
- Nationwide survey of breast cancer risk in blind women launched
- Establishment of an summer undergraduate volunteer program to assist in recruitment and data collection

REPORTABLE OUTCOMES

We have presented the protocol on two occasions in abstract (Appendix B and C) and poster format:

Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Dana-Farber/Harvard Cancer Center Cancer Disparities Program, New Investigators Poster Session; 2005; Apr 15; Boston, USA.

Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Era of Hope Department of Defense Breast Cancer Research Program Meeting; 2005; Jun 8-11; Philadelphia, USA.

We (Ms. Evans, Drs. Lockley, Schernhammer and Stevens) also attended the 'International Conference on Cancer and Rhythm: A new challenge in occupational medicine' in Graz, Austria in October, 2004, and Drs. Schernhammer and Stevens were speakers at the meeting.

CONCLUSIONS

Data collection is ongoing and there are no conclusions to report at this time. Confirmation of the inverse relationship between visual impairment and breast cancer risk and the identification of factors that account for the lower risk of breast cancer in blind women may result in health advice or therapies applicable to blind and sighted populations. Characterization of the potential role of endogenous melatonin rhythmicity in breast cancer risk is a required step towards clinical trials of melatonin administration as a treatment or preventative measure for breast cancer.

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Appendix A

SURVEY OF HEALTH AND SLEEP IN THE VISUALLY IMPAIRED
(v 4.4)

Date (e.g. 04 Aug 2005):_____ Time (24-hour clock hh:mm):_____

Research Assistant:_____ *(Only included in telephone/in-person surveys)*

GENERAL INFORMATION

1. Date of Birth (e.g. 04 Aug 1941): _____
2. Place of Birth (City, State, Country): _____
3. Gender (Male/Female): _____
4. Height (feet/inches): _____
5. Weight (pounds): _____
6. Weight at age 18 (pounds): _____

Current Address:

_____
_____
_____
_____
_____
_____

Telephone:_____ e-mail:_____

TTY/TDD:_____

Can you give details of another person to contact in case we are unable to find you?

Address:

_____
_____
_____
_____
_____
_____

Telephone:_____ e-mail:_____

TTY/TDD:_____

You may find that some question numbers appear to be missed as you go through the survey. This is because some questions may not be necessary based on the answers that you have given. We hope that this will save you time when completing the survey.

VISUAL IMPAIRMENT HISTORY

7. What is the name of the eye condition that caused loss of vision in your eyes?
   7a. Right Eye:_____
   7b. Left Eye:_____

8. Do you have any of the eye conditions listed below? (check the box).

8a. Right Eye:

___ "Dry" Macular Degeneration
___ "Wet" Macular Degeneration
___ Retinitis pigmentosa or other retinal dystrophies
___ Retinal detachment
___ Glaucoma
___Optic nerve disease
___Other eye disease

8b. Left Eye:

___ "Dry" Macular Degeneration
___ "Wet" Macular Degeneration
___ Retinitis pigmentosa or other retinal dystrophies
___ Retinal detachment
___ Glaucoma
___Optic nerve disease
___Other eye disease

8c. Have either of your eyes been enucleated (removed)?

___Yes Please state the reason for enucleation in your right and/or left eye.
___No

9. Do you have any other eye conditions?

___ No
___ Yes If yes, please list below.

9a. Right Eye: _____
_____
_____
_____
_____

9b. Left Eye: _____
_____
_____
_____
_____

10. What was your approximate age of onset of your visual loss?

10a. Right Eye:_____
10b Left Eye: _____

11. Are you registered as legally blind?

___ Yes 11a. If yes, approximate date of registration: _____
___ No

12. What was the rapidity of your visual loss?

12a. Right Eye:

___ N/A I have been blind since birth
___ I lost my vision instantly
___ I lost most of my vision over a period of few days
___ I lost most of my vision over a period of weeks
___ I lost most of my vision over a period of months
___ I lost most of my vision over a period of years

12b. Left Eye:

___ N/A I have been blind since birth

___ I lost my vision instantly
___ I lost most of my vision over a period of few days
___ I lost most of my vision over a period of weeks
___ I lost most of my vision over a period of months
___ I lost most of my vision over a period of years

13. What is the level of your vision?

13a. Right Eye:
___ Able to see the top letter on the vision chart
___ Unable to see the chart but can see to count fingers
___ Unable to count fingers but can see shadows and hand movement
___ Unable to see shadows but can see light
___ Unable to see light
If no light perception, date of onset of no light perception? _____

13b. Left Eye:
___ Able to see the top letter on the vision chart
___ Unable to see the chart but can see to count fingers
___ Unable to count fingers but can see shadows and hand movement
___ Unable to see shadows but can see light
___ Unable to see light
If no light perception, date of onset of no light perception? _____

14. How has your eye condition affected your field of vision?

14a. Right Eye:
___ I can only see in the periphery of my vision
___ I can only see in the center of my vision
___ I can see both in the periphery and center of my vision
___ I have no vision in the periphery or the center

14b. Left Eye:
___ I can only see in the periphery of my vision
___ I can only see in the center of my vision
___ I can see both in the periphery and center of my vision
___ I have no vision in the periphery or the center

15. Do you have a 'seeing-eye' dog or guide dog?
___ Yes
___ No

15a. Do you regularly wear either of the following:
___Scleral Shells/Cosmetic Contact Lenses
___Opaque Sunglasses

16. Do you ever see images that you know are not there?
___ Yes (if Yes, please continue)
___ No (if No, please got to Q32)

17. What kind of images do you see?
_____ Images of people that I recognize
_____ Images of people that I do not know. For example cowboys, soldiers, etc
_____ Images of objects. For example flowers, cars, others
_____ Images of Animals
_____ Non-formed images. For example color patterns, shadows, etc.
_____ Other images. Please specify:_____

18. On average, how often do you see these images?
_____ One or more times a day
_____ One to four times in a week
_____ One to four times in a month
_____ One to ten times in a year
_____ Once every few years

19. How long do these images stay visible?
_____ Up to 1 minute
_____ Up to 30 minutes
_____ Up to 3 hours
_____ Up to 24 hours
_____ More than 24 hours

20. What is the quality of these images?
_____ Black and white
_____ Vaguely colored
_____ Vividly colored
_____ Cannot tell

21. Are these images:
_____ Still (not moving, like a still photograph)
_____ Moving (like a movie)

22. Are these images
_____ Normal size
_____ Smaller than real life
_____ Larger than real life
_____ Cannot tell if smaller or larger

23. Do these images relate to somebody or something that you have seen in the past?
___ Yes
___ No

24. Do you have an aura (a feeling) before the images come on?
___ Yes
___ No

25. Do the images interfere with what you are doing or seeing?
___ Yes
___ No

26. When do you most frequently see these images
_____ In the morning
_____ During the day
_____ Early in the evening
_____ Late at night
_____ Anytime of the day

27. Do you tend to see these images mainly
_____ In dim illumination. For example in the evening.
_____ In bright illumination
_____ In any illumination

28. Do you see these images more frequently in the:
_____ Spring

_____ Summer
_____ Fall
_____ Winter
_____ No seasonal variation

29. Do you find these images
_____ Disturbing and stressful
_____ Not disturbing / stressful
_____ They were initially disturbing / stressful but got used to them and I am not bothered with them anymore
_____ Other: _____

30. Have you discussed these images with anyone?
_____ No. I did not think much of experiencing these images
_____ No. I was concerned about what other people may think about me
_____ Yes. I discussed the images with family / friends
_____ Yes. I discussed seeing these images with my doctor

31. Have you ever sought medical treatment for these visual experiences?
___ Yes
___ No

If yes, what kind of treatment? _____

IF YOUR CORRECTED VISION IS BETTER THAN THE ABILITY TO SEE THE TOP LINE OF THE VISION CHART, PLEASE DO NOT CONTINUE WITH THE SURVEY. THANK YOU.

MEDICAL HISTORY

32. Have you ever had or do you currently have any of the following chronic conditions?
At what age were you diagnosed?

_____Heart disease		Age_____[do not know]
_____Diabetes	Take insulin?_____Take pills?_____	Age_____[do not know]
_____Depression	Type?_____	Age_____[do not know]
_____Cancer	Type?_____	Age_____[do not know]
	Type?_____	Age_____[do not know]
	Type?_____	Age_____[do not know]
_____Benign breast disease (non-cancerous breast abnormality)		Age_____[do not know]
_____Other	Type?_____	Age_____[do not know]
_____No chronic conditions		

33. Have your parents ever had or currently have any of the following chronic conditions?
At what age were they diagnosed?

33a. Father

_____Heart disease		Age_____[do not know]
_____Diabetes	Take insulin?_____Take pills?_____	Age_____[do not know]
_____Depression	Type?_____	Age_____[do not know]
_____Cancer	Type?_____	Age_____[do not know]
	Type?_____	Age_____[do not know]
	Type?_____	Age_____[do not know]
_____Other	Type?_____	Age_____[do not know]
_____No chronic conditions		

33b. Mother

_____Heart disease Age_____[do not know]
_____Diabetes Take insulin?_____Take pills?_____ Age_____[do not know]
_____Depression Type?_____ Age_____[do not know]
_____Cancer Type?_____ Age_____[do not know]
Type?_____ Age_____[do not know]
Type?_____ Age_____[do not know]
_____Benign breast disease (non-cancerous breast abnormality) Age_____[do not know]
_____Other Type?_____ Age_____[do not know]
_____No chronic conditions

The following ten questions apply to the last two weeks.
Over the past two weeks, how often have you:

34. been feeling low in energy, slowed down?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

35. been blaming yourself for things?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

36. had poor appetite?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

37. had difficulty falling asleep, staying asleep?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

38. been feeling hopeless about the future?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

39. been feeling blue?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

40. been feeling no interest in things?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

41. had feelings of worthlessness?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

42. thought about or wanted to commit suicide?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

If the response to 42 is 'some of the time', 'most of the time', or 'all of the time'
42a. Do you have a plan?
___No
___Yes

If Yes, your response to the previous question causes us to be concerned for your welfare. While your response remains strictly confidential, we urge you to obtain medical evaluation locally. There are many programs available and we encourage you to contact a Mental Healthcare Professional in your area.

43. had difficulty concentrating or making decisions?
_____none or little of the time_____some of the time_____most of the time_____ all of the time

[*Please place underneath Qu 43:*
The preceding ten questions Copyright 1998 Harvard Department of Psychiatry and Screening for Mental Health]

44. Do you take any prescription medications on a regular basis?
___ No
___ Yes
If yes, please select which category or categories of drugs you take. You may chose multiple categories if applicable.

___Antidepressants
___Beta-blockers (heart and anxiety medication)
___Hypnotics (prescription sleep aids)
___Other medication

Antidepressants
Please check if you are taking any of the following:
_____Elavil, Etrafon, Limbitrol, Triavil or Amitriptyline HCl
_____Wellbutrin, Zyban or Buproprion HCl
_____Aventyl, Pamelor or Nortriptyline HCl
_____Celexa or Citalopram
_____Lexapro or Escitalopram Oxalate
_____Prozac, Sarafem or Fluoxetine HCl
_____Paxil or Paroxetine HCl
_____Zoloft or Sertraline HCl
_____Desyrel or Trazodone HCl
_____Effexor or Venlafaxine HCl
_____Other:_____

Beta-Blockers (heart and anxiety medication)
Please check if you are taking any of the following:
_____Tenormin or Atenolol
_____Betopic, Kerlone or Betaxolol
_____Ziac or Bisoprolol/hydrochlorothiazide
_____Ocupress, Cartrol or Carteolol
_____Coreg or Carvedilol
_____Lopressor, Toprol or Metoprolol Tartrate
_____Corgard or Nadolol
_____Inderal or Propranolol HCl
_____Blocadren or Timolol Maleate
_____Other:_____

Hypnotics (prescription sleep aides)
Please check if you are taking any of the following:
_____Ambien or Zolpidem Tartrate
_____Sonata or Zaleplon
_____Dalmane, or Flurazepam HCl
_____Restoril orTemazepam
_____Halcion or Triazolam
_____Ativan or Lorazepam
_____Xanax or Alprazolam
_____Zopiclone
_____Secobarbital Sodium or Seconal Sodium Pulvules
_____Pentobarbital Sodium or Pentobarbital Sodium or Nembutal
_____Other:_____

Other medication

_____Corticosteroids (e.g. prednisolone, prednisone, Decadron, Medrol, steroid inhalors)

_____Drugs to control inflammation pain (for example Celebrex, Aspirin, Aleve, Naprosyn, Relafen, Ketoprofen, Anaprox)

_____Calcium blocker (e.g. Calan, Procardia, Cardizem)

_____ACE inhibitor (e.g. Capoten, Vasotec, Zestril)

_____Diuretic (e.g. Lasix)`

_____ "Non-drowsy" antihistamines (e.g., Allegra, Astelin, Clarinex, Claritin, Zyrtec)

_____"Drowsy" antihistamines (e.g. Atarax, Benadryl, Bromphen, Gravol, Periactin, Tavist, Zadine)

_____Check here if you take prescription drugs other than those listed above.
Please list all additional drugs that you are taking.

_____
_____
_____
_____
_____
_____

45. Do you currently smoke?

___ No [please go to Q46]
___ Yes

45a. If yes, how many cigarettes or cigars do you smoke per day?
___ Number of cigarettes
___ Number of cigars [please go to Q47]

46. Have you ever smoked?

___ No
___ Yes

46a. If yes, how many cigarettes or cigars did you smoke per day?
___ Number of cigarettes
___Number of cigars

47. How many years in total have you smoked, up to today?_____

REPRODUCTIVE HISTORY [IF MALE, PLEASE GO TO Q61]

48. How old were you when you started puberty?_____
(Defined as age when you had your first period)

49. Are you still having periods or are you in menopause or post-menopause?

___ Periods (Please go to Q50)
___ In menopause (Please go to Q51)
___ Post-menopause (Please go to Q51)

50. Over the past six months, on average, what has been the usual length of your menstrual cycle (i.e., from the 1st day of one period up to but not including the 1st day of your next period?

___ <21 days (Please go to Q56)
___ 21-25 days (Please go to Q56)
___ 26-31 days (Please go to Q56)
___ 32-39 days (Please go to Q56)
___ 40-50 days (Please go to Q56)
___ >=51 days (Please go to Q56)
___ too irregular to estimate (Please go to Q56)

If in menopause or post-menopause...

51. How old were you when you began to experience menopausal symptoms such as regularly missed periods, intermittent bleeding, hot flashes?_____

52. How old were you when your periods stopped completely?_____

53. Was the onset of your menopause natural i.e., not drug- or surgery-induced?

___ Natural
___ Medical
___ Surgical
53a. If due to a medical or surgical condition, what was the reason?_____
___ Other_____

54. Have you been or are you on Hormone Replacement Therapy/HRT?

___ No
___ Yes
54a. What month and year did you start?_____
54b. How is/was the HRT administered?
___ by mouth
___ from patches
54c. Are you currently taking HRT?
___ Yes
___ No
54d. If No, what month and year did you stop?_____

54e. What type have you used for the longest?
___ Progesterone / estrogen combination
___ Estrogen only
___ Progesterone only /Progestin
___ Other
___ I do not know

54f. Please provide the brand name if possible_____

55. Have you had any ovaries or your uterus removed?

___ No
___ Yes

55a. If yes,
___ One ovary At what age? _____
___ Both ovaries At what age? _____
___ Uterus At what age? _____

56. Have you ever or do you currently use oral contraceptives?

___ No
___ Yes

56a. What month and year did you start?_____
56b. Are you currently taking oral contraceptives?
___ Yes
___ No
56c. If No, what month and year did you stop?_____
56d. What type have you used for the longest?
___ Progesterone / estrogen combination
___ Estrogen only
___ Progesterone only /Progestin
___ Other
___ I do not know

56e. Please provide the brand name if possible_____

57. Have you ever been pregnant?
___ No (If No, please go to Q59)
___ Yes

57a. If yes, did any of your pregnancies not run full-term?
___ Yes
___ No

57b. If Yes, why did the pregnancy(s) not run full term?
___ Miscarriage
___ Termination
___ Other

58. How old were you at your first full term pregnancy?_____

59. How many pregnancies have you had?_____

60. Did you ever breast-feed your children?
___ No
___ Yes

DIET OVER THE PAST YEAR

61. If you had to place your diet in one category, would you say that it's more Eastern (traditional Asian foods such as rice and beans/ soy- or grain-based), Mediterranean (pasta, bread), or Northern European (meat and potatoes), Vegetarian, or Vegan?
___ Eastern
___ Mediterranean
___ N. European
___ Vegetarian
___ Vegan

62. What percentage (0-100%) of your diet is carbohydrates (for example, starchy foods such as white potatoes, pasta, bread, soft drinks or soda, cakes, cookies, quick breads and doughnuts, sugars, syrups, jams, white potatoes, ready to eat cereals, milk)? _____

63. From all carbohydrates you eat, what percentage (0-100%) are whole grain foods, such as whole wheat

pasta, brown rice, whole grain bread, etc?_____

64. In terms of portion size and number of portions, would you classify yourself as a light eater, average eater, or heavy eater?

___ Light
___ Average
___ Heavy

65. Do you typically eat the following meals at the same time every day (within 30 minutes)?

Breakfast	___ No
	___ Yes
Lunch	___ No
	___ Yes
Dinner	___ No
	___ Yes

66. Are you presently on a reduced calorie diet to lose weight?

___ No
___ Yes

67. Do you take any vitamins, supplements, or dietary pills?

___ No
___ Yes

68. Do you take melatonin tablets?

___ Yes
___ No

68a. If No, have you taken melatonin tablets in the past?

___ Yes
___ No

69. How many drinks of alcohol do you usually have per week?
(1 drink = 1 can/bottle/glass of beer, 1 glass of wine, 1 shot of liquor)

_____x 1 can/bottle/glass of beer
_____x 1 glass of wine
_____x 1 shot of liquor

70. At what time of day do you usually drink most alcohol?

_____Not applicable –I don't drink alcohol
_____Morning
_____Lunchtime
_____Afternoon
_____During dinner
_____After dinner
_____No preference

71. What time of year do you usually drink most?

_____Not applicable –I don't drink alcohol
_____Spring
_____Summer
_____Fall
_____Winter
_____No seasonal difference

72. How many drinks of alcohol did you usually have per week when you were 21 years old?

(1 drink = 1 can/bottle/glass of beer, 1 glass of wine, 1 shot of liquor)_____

73. How many caffeine-containing drinks do you usually have per day?
_____Coffee (cups)
_____Tea (cups)
_____Hot chocolate (cups)
_____Decaffeinated tea or coffee (cups)
_____Caffeinated soda (Coke, Pepsi, Mountain Dew) (cans)
_____Caffeinated energy drinks (Red Bull, Venom, Adrenaline Rush, 180, ISO Sprint, Whoopass, Semtex) (cans)

74. At what time of day do you usually drink most caffeine?
_____Not applicable –I don't drink caffeine
_____Morning
_____Lunchtime
_____Afternoon
_____During dinner
_____After dinner
_____No preference

75. Do you take caffeine pills regularly?
___ No
___ Yes

PHYSICAL ACTIVITY

76. How many hours a week do you spend doing each of the following recreational activities?
___ Walking to exercise or walking to work
___ Walking a dog
___ Jogging/running
___ Bicycling, including bike machine
___ Swimming
___ Other aerobic exercises e.g. aerobics, stair machine, ski machine
___ Lower intensity exercise e.g. yoga, stretching, toning
___ Other vigorous activities e.g. lawn mowing
___ Weight training or resistance exercises, including free weights or machines

WORK HISTORY

77. Current employment status
_____Full-time
_____Part-time
_____Full-time homemaker
_____Student
_____Retired
_____Unemployed

78. Current occupation:_____

79. Do you currently work shifts?
___ No
___ Yes

79a. Which type of shifts do you currently work?
Days (e.g., 7am – 3pm) No___Yes___

If Yes, how many of these shifts do you work each month?_____
If Yes, how many years have you worked these shifts?_____
Evenings (e.g., 3pm – 11pm) No___Yes___
If Yes, how many of these shifts do you work each month?_____
If Yes, how many years have you worked these shifts?____
Night/Graveyard shift (e.g., 11pm - 7am) No___Yes___
If Yes, how many of these shifts do you work each month?_____
If Yes, how many years have you worked these shifts?_____

80. Have you worked shifts in the past?
___ No
___ Yes

80a. How many years of your working life have you worked any of the following shifts:
_____Days (e.g., 7am – 3pm)
How old were you when you started working these shifts?_____
On average, how many of these shifts did you work each month?_____
_____Evenings (e.g., 3pm – 11pm)
How old were you when you started working these shifts?_____
On average, how many of these shifts did you work each month?_____
_____Night/Graveyard shift (e.g., 11pm - 7am)
How old were you when you started working these shifts?_____
On average, how many of these shifts did you work each month?_____

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

The following ten questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all the questions.

81) During the past month, when have you usually gone to bed at night?
Usual bed time _____

82) During the past month, how long (in minutes) has it usually take you to fall asleep each night?
Number of minutes _____

83) During the past month, when have you usually got up in the morning?
Usual getting up time _____

84) During the past month, how many hours of actual sleep did you get at night? (This may be different from the number of hours spent in bed.)
Hours of sleep per night_____

For each of the remaining questions, check the one best response. Please answer *all* questions.

85) During the past month, how often have you had trouble sleeping because you.....

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Have pain

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

j) Other reason(s), please describe _____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

86) During the past month, how would you rate your sleep quality overall?

_____Very good
_____Fairly good
_____Fairly bad
_____Very bad

87) During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

88) During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

89) During the past month, how much of a problem has it been for you to show enthusiasm to get things done?

_____No problem at all
_____Only a very slight problem
_____Somewhat of a problem
_____A very big problem

90) Do you have a bed partner or roommate?

No bed partner or roommate?_____
Partner/roommate in other room_____

Partner in same room, but not same bed_____
Partner in same bed_____

SLEEP QUESTIONS

91. Do you fall asleep during the day?
___ Never
___ Rarely
___ Often
___ Usually

92. Do you have any difficulty getting up in the mornings?
___ No
___ Yes

93. Do you go through periods of good sleep and periods of bad sleep?
___ No
___ Yes

91b. If yes, do you go through phases of getting to sleep or waking up
___ later and later
___ earlier and earlier

94. Is your sleep pattern cyclic?
___ No
___ Yes

94a. If yes, how many weeks does it take to complete one cycle (i.e. the number of weeks from a period of good sleep to the next period of good sleep)._____

95. How often do you get up and turn on a light at night?
___ Never
___ Rarely
___ Often
___ Usually

96. Do you ever skip a night's sleep?
___ No
___ Yes

97. Do you feel that your sleep pattern has changed since the deterioration of your vision?
___ No
___ Yes
___ Not applicable

98. Is your sleep pattern different during work-free periods (e.g. vacations, weekends)?
___ No
___ Yes
___ Not applicable

99. Does your sleep pattern affect your social or occupational life?
___ No
___ Yes

100. Do you fall asleep during the following activities?
Traveling in car/bus/train No___Rarely___Often____

Watching/listening to TV/radio	No	Rarely	Often
During meals	No	Rarely	Often
During meetings	No	Rarely	Often
During conversations	No	Rarely	Often

101. Do you do anything to help you sleep and does it work?

_____Relaxation/breathing techniques	Does it work? No	Yes	Sometimes
_____Hot drink	Does it work? No	Yes	Sometimes
_____Hot bath	Does it work? No	Yes	Sometimes
_____Alcohol	Does it work? No	Yes	Sometimes
_____Prescription medications	Does it work? No	Yes	Sometimes
_____Over-the-counter medications	Does it work? No	Yes	Sometimes
_____Other?	Does it work? No	Yes	Sometimes

101a. What types of other things do you do to help you sleep?

102. You may have heard about "morning" and "evening" type people who prefer to do physical, difficult or concentrated tasks at particular times of the day. Which one of these types do you consider yourself to be?

___ Definitely a "morning" type
___ Rather more a "morning" than an "evening" type
___ Rather more an "evening" than a "morning" type
___ Definitely an "evening" type?

103. Do you notice a drop in your energy in the fall and winter compared to the spring and summer?

___ Yes, a lot
___ Yes, a little
___ No, energy stays about the same
___ No, energy increases

104. Do you tend to sleep more, or eat more sweet or starchy foods, in the fall and winter compared to the spring and summer?

___ Yes, a lot
___ Yes, a little
___ No, sleep and appetite stay about the same.
___ No, sleep or appetite diminish in the fall and winter.

105. Do you feel sadder and enjoy things less in the fall and winter compared to the spring and summer?

___ Yes, a lot
___ Yes, a little
___ No, I feel about the same in the fall and winter.
___ No, I feel better and enjoy things more in the fall and winter.

106. Do you have a lot of friends?

___ Yes, I have many friends
___ I have a few friends
___ I do not have enough friends
___ I do not have any friends

107. Do you feel lonely a lot of the time?

___ No, I am too busy
___ Sometimes I feel lonely
___ Yes, I am usually lonely

GENERAL DEMOGRAPHICS

108. What is your major ancestry?
___ Non-Hispanic or Latino
___ Hispanic or Latino

108a. If Hispanic or Latino, what is your family origin:
___ Cuba
___ Mexico
___ Portugal
___ PR
___ South America
___ Spain

109. Which best describes your ethnicity?
___ White
___ Black or African American
___ Asian
___ Native Hawaiian or Other Pacific Islander
___ American Indian / Alaskan Native
___ Other

110. Current marital status
_____Single and never married
_____Living with a partner
_____Married
_____Divorced
_____Separated
_____Widowed

111. Current living arrangements
_____Alone
_____With spouse/partner
_____With other family
_____With roommates
_____Other

112. How many children do you currently live with, if any?_____

113. Do you meet friends and family often?
___ Rarely
___ Often
___ Very often

114. Do you belong to a volunteer organization?
___ Yes
___ No

115. Are you active in a church?
___ Yes
___ No

116. What was the highest level of school you completed?
_____K-8
_____Some High School

_____High School graduate
_____Tech school/Assoc.
_____Some college
_____College graduate Degree?_____
_____Post-college Degree?_____

117. What is your approximate family income from all sources?
_____Less than $20,000
_____$20,000-$30,000
_____$30,000-$50,000
_____$50,000-$75,000
_____$75,000-$100,000
_____More than $100,000

CONTACT DETAILS

118. Where did you find out about the study?_____

119. May we contact you to do a follow-up survey in the future?
___ No
___ Yes

120. May we contact you about other future studies?
___ No
___ Yes

Appendix B: Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Dana-Farber/Harvard Cancer Center Cancer Disparities Program, New Investigators Poster Session; 2005; Apr 15; Boston, USA.

REPRODUCTIVE AND HORMONAL RISK FACTORS FOR BREAST CANCER IN BLIND WOMEN

Erin E. Evans, R.Psg.T. (1), Eva S. Schernhammer, M.D., Dr.P.H. (2), Eve S. Silver B.C.S. (3), Richard G. Stevens, Ph.D. (4), Steven W. Lockley, Ph.D. (1,5)

(1) Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA; (2) Channing Laboratory, Department of Medicine and Brigham and Women's Hospital, Harvard Medical School, Boston, MA; (3) Cinta Latina Research, Red Bank, NJ; (4) Division of Epidemiology and Biostatistics, University of Connecticut Health Center, Farmington, CT; (5) Division of Sleep Medicine, Harvard Medical School, Boston, MA.

Epidemiological observations indicate that the risk of certain types of cancer, particularly breast cancer in women, is reduced by as much as 40% in people who are totally blind compared to the sighted population, and that risk may be inversely correlated with degree of visual impairment. We are about to launch a nationwide survey of ~12,000 blind women to examine breast cancer risk factors, including questions on medical and reproductive history, visual impairment, circadian sleep disorders, and lifestyle.

Frequent suppression of pineal melatonin production by light exposure at night has been hypothesized as a major contributor to the higher breast cancer incidence observed in female shiftworkers. Melatonin has been shown to have oncostatic properties in vitro and it has been proposed that blind people are less susceptible to melatonin suppression and are thus protected by higher circulating levels of melatonin. We will address how the severity of blindness relates to melatonin production and other known risk factors for breast cancer by measuring 24 h rhythms of urinary melatonin and estrogen metabolites in 240 participants and evaluating associations with breast cancer risk factors as assessed by the survey, to examine other potential explanations including changes in the circadian system and altered reproductive function.

Appendix C: Evans EE, Schernhammer ES, Silver ES, Stevens RG, Lockley SW. Reproductive and hormonal risk factors for breast cancer in blind women. Era of Hope Department of Defense Breast Cancer Research Program Meeting; 2005; Jun 8-11; Philadelphia, USA.

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Epidemiological observations indicate that the risk of certain types of cancer is significantly lower in people who are visually impaired as compared to the sighted population and that risk may be inversely correlated with degree of visual impairment. One hypothesis proposed to explain these findings is that blind people are less susceptible to suppression of melatonin by light exposure at night and therefore have higher circulating levels of melatonin. Melatonin has been shown to have oncostatic properties in vitro. Frequent light-induced melatonin suppression has been hypothesized as a cause of the higher breast cancer incidence observed in female shiftworkers and flight-attendants. Preliminary data suggest, however, that melatonin levels are not elevated in the blind. Blindness is also associated with disorders of the circadian system and changes in reproductive function which may also contribute to breast cancer risk. The aim of this study is to investigate further the relationship between the severity of blindness and melatonin production while simultaneously assessing how blindness and/or melatonin production are related to known risk factors for breast cancer.

The study will consist of an epidemiological health survey in 12,000 blind women, including questions on breast cancer risk factors, medical and reproductive history, visual impairment, circadian sleep disorders, and lifestyle factors. In a subset of 240 women, we will measure 24 h rhythms of urinary melatonin and estrogen metabolites in addition to detailed assessments of circadian rhythms sleep disorders in a two-month field study.

We will test the hypotheses that 1) the distribution of known reproductive risk factors for breast cancer among blind women, for example, age at menarche, age at menopause and age at first birth, will be consistent with a lower breast cancer risk in blind women (e.g. later age of menarche, earlier age of menopause, earlier age at first birth) when compared to the general population; 2) melatonin levels are significantly lower and estrogen levels are significantly higher among visually impaired women with some degree of light perception compared to women with no light perception; 3) melatonin levels will be significantly higher and estrogen levels will be significantly lower among totally blind women who have non-24-hour melatonin and sleep-wake rhythms and therefore a confirmed absence of light-induced suppression of melatonin, compared to totally blind women who have 24-hour melatonin and sleep-wake rhythms and may be affected by light exposure.

Confirmation of the inverse relationship between visual impairment and breast cancer risk and the identification of factors that account for the lower risk of breast cancer in blind women may result in health advice or therapies applicable to blind and sighted populations. Characterization of the potential role of endogenous melatonin rhythmicity in breast cancer risk is a required step towards clinical trials of melatonin administration as a treatment or preventative measure for breast cancer.

The U.S. Army Medical Research and Material Command under W81XWH-04-1-0553 supported this work.